ImmunoTools *multiplex* Award 2016

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Identification of (novel) immunological markers to characterize the disease status of septic patients

Sepsis is a severe syndrome causing thousands of deaths worldwide. As generally accepted definition, sepsis is triggered by systemic infections, which cause immune pathology due to uncontrolled immune responses. These "uncontrolled immune responses" can be divided into two phases: The first phase is characterized by "overwhelming, uncontrolled inflammation" (SIRS, systemic inflammatory response syndrome), often causing septic shock. The second phase, occurring subsequently or even in parallel is called CARS (compensatory anti-inflammatory response syndrome). Septic patients suffering from "immune paralysis" often succumb to opportunistic infections (*Hotchkiss and Karl, 2003; Hotchkiss and Sherwood, 2015*). While the first phase is increasingly under medical control, the second phase is hardly understood and causes most of the deaths (*Hotchkiss et al., 2009; Hotchkiss and Sherwood, 2015*).

The major problem of sepsis is that currently a correct diagnosis of septic patients is not possible. Due to the absence of (good) markers, it is hard to determine whether patients suffer from SIRS, CARS or a combination of both. Over many decades, most research has concentrated on the early, first phase. Animal models and clinical trials have been devoted to mimic septic shock (LPS, CLP, CASP) to identify inflammatory mediators (e.g. TNF, IL-1) and to develop treatments (e.g. anti-TNF etc.) (*Hotchkiss and Sherwood, 2015; Ward, 2015; Hutchins, 2014).* While unfortunately all clinical trials in this direction have failed so far (*Hutchins et al., 2014; Ward 2014*), currently trials are designed or already ongoing, which test stimulatory approaches to overcome immune suppression (e.g. GMCSF) (*Meisel et al.2009; Hutchins et al., 2014*).

We have currently reported (*Schäfer et al., 2016*) that septic immune paralysis can be triggered not only by infections but also by mitochondrial DNA (mtDNA) a DAMP (damage associated molecular pattern) so far reported to cause inflammation (*Zhang et al., 2010*). In our study we demonstrate that sepsis can occur in the absence of an infectious agent and that

the TLR9-Ligand mtDNA can suppress adaptive immunity. We could identify various suppressive mechanisms: in serum we detected the up-regulation of IDO activity, while in spleen PDL1 was up-regulated, cross-presenting DCs were deleted and the marginal zone was destructed (in human septic patients as well as mice). Most importantly, the level of mtDNA and the soluble IL-2receptor (sIL-2R) in septic patients strongly correlated with disease severity, thus representing two potential new markers for diagnosing sepsis.

To identify new, so far unknown markers for the diagnosis of SIRS and immune paralysis in sepsis, we would like to apply for the ImmunoTools multiplex award. With the help of this array we think that further markers could hopefully be identified.

References:

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